UNITED STA[redacted] DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/559,707	04/27/00	GREENWOOD J	19141-002

EXAMINER	
LOEB, B	
ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 03/28/01

HM12/0328

IVOR R ELRIFI
C/O MINTZ LEVIN
ONE FINANCIAL CENTER
BOSTON MA 02111

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/559,707	GREENWOOD ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *08/973,553* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

The as-filed claims had duplicate claim numbers. Specifically, the claims presented were numbered 1-34, 29 and 30. These last two claims were renumbered 35 and 36, respectively, under 37 C.F.R. 1.126. Claims 1-36 are pending.

Oath/Declaration

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

It is also noted that part of the signature page is obscured.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Upon review of the specifications of the parent applications and comparison with the specification of the instant application, it is determined that the specifications of parent applications 09/182,516, 08/973,553, and FR9604964 are ***not*** enabling for the preparation of the claimed invention in the instant application. The specifications of these parent applications do ***not*** teach or suggest cell lines comprising cells comprising human telomerase reverse transcriptase gene (hTRT) or a sequence able to activate an endogenous hTRT gene, or cells subjected to spontaneous genetic mutation leading to an extended life-span, or methods using such cell lines. The parent applications are *entirely silent* regarding cells comprising hTRT or a sequence able to activate an endogenous hTRT or cells comprising a spontaneous genetic mutation leading to an extended life-span. Since such cell lines and methods of using them are not disclosed in the parent applications and cannot be predicted from the teachings of the parent applications, the parent applications are not enabling for the claimed inventions of the instant application. Thus, the requirements of the first paragraph of 35 U.S.C. 112 have not been satisfied. Therefore, the priority date for claims 1-35 as they read on hTRT or spontaneous genetic mutations is the filing date of the instant application, April 27, 2000. The priority date for claims 1-35 as they read on oncogenes is April 19, 1996.

Specification

2. The disclosure is objected to because of the following informalities: Figures 1-7, 12, 13, 17, 20, 23 and 25-32 contain multiple panels however the Brief Description of the Drawings does not clearly reflect that. It would be remedial to amend the specification, for example, on p. 4, line 27, to read "Figures 1A-1D are".

There are abbreviations used without definitions provided, for instance, IFN γ and TNF α.

On p. 21, lines 18-19, the statement regarding OX-43 expression in aortic EC does not agree with the data in Table 1.

On page 26, line 15, the meaning of the phrase "<<face-on>>" is unclear.

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Not all of the polypeptides recited in claims 17 and 18 have proper antecedent basis in the specification. These polypeptides include: neurotrophins, interleukins, antigens, and all of the polypeptides recited in the Markush group of claim 18.

Appropriate correction is required.

Claim Objections

4. Claims 8, 10, 11, 18, 19, 20, 33 and 35 are objected to because of the following informalities: Claims 8 and 33 recite lines whose names (IO/LD7 and IO/JG1) do not correspond exactly to the names of the cell lines deposited in the CNCM (see for instance p. 12 and the Brief Description of the Drawings). Claims 10, 11, and 18 recite abbreviations without providing definitions. Abbreviations should be defined at their first use in the claims. In claim 19, line 3 the preposition "in" is missing in the phrase "introducing to the cells". Also, in claim 19, the phrase "and combinations thereof" in line 12 is redundant since step (e) initially recites "selecting a passaged cell line that has

at least one mammalian retinal pigment epithelial characteristic" (emphasis added). In claim 20, step (a) line 2, the word "selected" is misspelled. Claim 35 has two periods, one at the end of line 3 and one at the end of line 5.

Appropriate correction is required.

Double Patenting

5. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

6. Claim 8 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 2 of prior U.S. Patent No. 6,183,735 B1. This is a double patenting rejection.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1, 16, 19, 20, 25-26, 31 and 32 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 9-11 and 13 of U.S. Patent No. 6,183,735 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the issued patent are directed to species that are encompassed by the genus claims of the instant application.

9. Claims 1, 3-6, 9 and 12-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-7, 9 and 10 of U.S. Patent No. 6,090,624. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the issued patent are directed to species, which are encompassed by the genus claims of the instant application.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1, 7, 9-31 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 35 are drawn to a cell line wherein the cells of the cell line may be selected from "cells

subjected to a spontaneous genetic modification leading to an extended life-span" or "cells comprising a sequence able to activate the endogenous hTRT gene". Claims 19, 20 and 25 are drawn to methods comprising the step of introducing into the cells "a sequence able to activate the hTRT endogenous gene". Claim 24 is drawn to a method using "cells subjected to a spontaneous genetic modification leading to an extended life-span". Claim 30 is drawn to a method of using "cells subjected to a spontaneous genetic modification leading to an extended proliferation capacity". Claim 31 is drawn to a cell line wherein the cells of the cell line may be selected from cells comprising "a sequence able to activate the hTRT endogenous gene". These are genus claims with respect to any spontaneous genetic modification which leads to an extended life-span or extended proliferation capacity of the cell line and any sequence able to activate an endogenous hTRT gene. The specification does not describe in detail any such cells or the details of the genetic modification. Nor does the specification describe any sequences able to activate an endogenous hTRT gene, or cells containing such a sequence. This disclosure is not deemed to be descriptive of the complete structure of the representative number of species encompassed by the claims as one of skill in the art cannot envision all of the genetic modifications or the sequences able to activate an endogenous hTRT gene based on the teachings in the specification. There is no disclosure of a correlation between particular spontaneous genetic modifications and the capacity to extend life-span or proliferation capacity. There is no disclosure indicating what sequences are likely to activate an endogenous hTRT gene, or ways to go about defining such sequences. Therefore, the specification does not describe the

claimed cells in such full, clear, concise and exact terms so as to indicate that applicants had possession of these cells at the time of filing of the present application. Thus, the written description requirement has not been satisfied.

11. Claims 22, 23 and 26 are rejected under 35 U.S.C. 112, first paragraph, as ontaining subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad. Claims 22 and 23 are directed to a method of producing any polypeptide to treat any primary or secondary ophthalmologic or neurological disorders wherein cells comprising any expression vector encoding a therapeutic polypeptide are implanted in the eye of any mammalian host. Claim 26 is directed to a method of treating any primary or secondary ophthalmologic or neurological disorder comprising grafting mammalian host cells in the eye of any mammalian host wherein said host cells comprise any expression vector encoding a therapeutic polypeptide. The therapeutic polypeptide may be any polypeptide, the cells may be from any mammal, and they may be implanted in any mammal.

The nature of the invention is a method of treatment using a cell line comprising a recombinant polynucleotide and an expression vector encoding a therapeutic polypeptide. The delivery of a polynucleotide in vivo or ex vivo for therapeutic purposes constitutes gene therapy.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389: 239-242) and Anderson (Nature (1998) 392: 25-30) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Anderson, p. 25, col. 1, 1st paragraph. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. For instance, regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency of delivery and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Litchfield et al (Exp. Eye Res. (1997) 64: 655-666) specifically discuss the problems related to gene therapy and eye disorders; the problems include short-lived expression and the factor of unknown immunological consequences. See p. 662, 1st column, 1st and 2nd complete paragraphs. While all these references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique.

The relative skill of those in the art of recombinant cell lines is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic death of a participant in a gene therapy clinical trial clearly illustrates the unpredicatable nature of gene therapy. See Fox, (Feb. 2000) ASM News, Vol. 66 (2): 1-3.

The present specification provides little direction or guidance to support the claimed invention. The specification discloses that virtually any therapeutic polypeptide may be used and a large variety of ophthalmologic or neurologic diseases may be treated. There is little or no guidance on what polypeptides to use to treat what diseases. Furthermore, little or no direction is provided as to how to overcome the obstacles to gene therapy recognized by the leaders in the field, and particularly related to treating eye disorders, i.e. transient gene expression and unknown immunological consequences.

Working examples are disclosed wherein cells from a rat cell line without an expression vector encoding a therapeutic polypeptide are implanted into rat eyes (Ex. 4). In Ex. 9, cells from a human cell line without an expression vector encoding a therapeutic polypeptide were grafted subcutaneously in the flanks of nude mice, which were irradiated to preclude interference from immune competant cells. In Ex. 10, cells from a human cell line without an expression vector encoding a therapeutic polypeptide were implanted into the eyes of rats. Thus, the examples do not represent the claimed invention.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine what effect exogenous transgene expression would have in the mammalian host eye, whether the effect could be exploited for treatment of a disease, and how to achieve sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to answer them.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how use the claimed methods of treatment using cell lines comprising a polynucleotide and an expression vector encoding a therapeutic polypeptide.

12. Claims 1, 7, 9, 16-18, 24, 30 and 35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the

predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are broad. Claim 1 is drawn to a mammalian retinal pigment epithelial cell line wherein the cells are subjected to a spontaneous genetic modification leading to an extended life-span. Claims 24 and 30 are drawn to a method of producing a therapeutic polypeptide to treat primary or secondary ophthalmologic or neurological disorders which uses the cell line of claim 1. Claim 35 is drawn to a mammalian retinal endothelial cell line wherein the cells are subjected to a spontaneous genetic modification leading to an extended life-span. The spontaneous genetic modification may be of any sort which leads to an extended life-span.

The nature of the invention is a non-tumorigenic cell line having a spontaneous genetic modification leading to an extended life-span, and methods of using such a cell line to treat a wide variety of disorders.

An analysis of the prior art as of the effective filing date of the present application shows that cell lines commonly arise from spontaneously but the genetic modification underlying the change in phenotype is unknown. It is unclear what conditions specifically foster spontaneous genetic modifications generally, let alone those which result in an extended life-span **and** non-tumorigenicity for retinal pigment epithelial or endothelial cell lines.

The relative skill of those in the art of mammalian retinal pigment epithelial and endothelial cell lines is high.

The area of the invention is unpredictable. By definition, a spontaneous mutation is one for which there is no explanation. Thus, one is unable to predict the when, how, why and of what sort for such a mutation. Neither is one able to predict the replicable circumstances that generate a spontaneous genetic modification which leads to cells with an extended life-span, yet are not tumorigenic. Possibly such a spontaneous genetic modification is related to the specific donor eye used to culture cell lines (see p. 156 of Dunn et al (Exp. Eye Res. (1996) 62:155-169)). Given the unique source, it is unlikely one would be able to reproduce such a cell line, nor can one predict what about that donor eye allowed the development of the spontaneous genetic modification.

The present specification provides little or no guidance to support the claimed invention. There are no teachings regarding what it means to subject cells to a spontaneous genetic modification, or how to do this. Furthermore, there are no teachings regarding how to subject cells in such a way that the spontaneous genetic modification leads to both an extended life-span and non-tumorigenicity.

There is a working example demonstating the method of treating RCS rats with cells possessing such a spontaneous genetic modification. However, there are no working examples demonstrating how to subject cells to a spontaneous genetic modification which leads to extended life-span and non-tumorigenicity to develop such a cell line for use in such a treatment method.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled individual could not rely on the prior art or the present specification to teach how to make the claimed cell line and how to use the claimed method. In order to

make such a cell line having a spontaneous genetic modification, one would have to determine what types of genetic modification serve to extend life-span and further define among those the mutations which also are non-tumorigenic. One would then have to determine the conditions that foster such spontaneous genetic modifications. Thus, in order to answer these questions, one of skill in the art would have to resort to a large quantity of trial and error experimentation.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine make the claimed cell line wherein the cells are subjected to a spontaneous genetic modification leading to an extended life-span and non-tumorigenicity, and how to use the claimed method using such cell lines.

13. Claims 10 and 11 are drawn to specific human retinal pigment epithelial cell lines. Because it is not clear that the identical cell lines are freely available or can be reproducibly isolated from nature, a biological deposit of the recited cell lines for patenting purposes is required.

The requirements for description and enablement may be met by depositing the cell line in a recognized depository. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant or a statement by an attorney of record over his or her signature and registration number, stating that the specific material has been deposited under the Budapest Treaty and that the material

will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit is not made under the Budapest Treaty, then in order to certify that the deposit meets the requirements of 37 CFR 1.801-1.809 (see Federal Register, Vol. 54, No. 161, issued August 2 1989), Applicant may provide assurance of compliance by an affidavit or declaration or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;
(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
(d) the deposit will be replaced if it should ever become inviable.

Applicant must furthermore submit a viability statement consisting of:

(1) the name and address of the depository;
(2) the name and address of the depositor;
(3) the date of deposit;
(4) the identity of the deposit and the accession number given by the depository;
(5) the date of the viability test;
(6) the procedures used to obtain a sample if the test is not done by the depository; and
(7) a statement that the deposit is capable of reproduction.

A viability statement is not required for deposits made under the Budapest Treaty.

14. Claims 20, 21 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a polypeptide comprising incubating cells of a mammalian retinal pigment epithelial cell line in a biological compatible medium in vitro, does not reasonably provide enablement for a method of producing a polypeptide comprising incubating cells of a mammalian retinal pigment epithelial cell line in a biological compatible medium in vivo in a mammalian host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. These claims are broad, encompassing the treating primary or secondary ophthalmologic or neurological disorders by using a recombinant cell line in vivo to produce a therapeutic polypeptide, wherein the polypeptide may be any therapeutic polypeptide. As discussed above, neither the prior art nor the present specification provide enablement for methods of gene therapy. Therefore, based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how use the claimed methods of producing a therapeutic polypeptide in vivo using a recombinant cell line to treat primary or secondary ophthalmologic or neurological disorders.

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because the Markush group has only one member: cells. It would be remedial to amend each of (i), (ii) and (iii) to start with the word "cells" and to delete "cells" from line 3.

Claims 1, 19, 20, 25 and 31 recite the limitation "a sequence able to activate the endogenous hTRT gene" which is vague and indefinite. The phrase "able to activate" indicates a latent activity which may or may not be present in the invention. Furthermore, it is unclear whether the sequence itself activates the endogenous gene or if a product encoded by the sequence activates the gene.

Claim 1 recites the limitation "the human telomerase reverse transcriptase gene" in lines 7-8. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 is vague and indefinite because it is unclear if the oncogene product is heat sensitive or if the expression of the oncogene is heat sensitive.

Claim 3 is vague and indefinite because it is unclear if the oncogene product is non-thermosensitive or if the expression of the oncogene is non-thermosensitive.

Claim 5 recites the limitation "oncogenes" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 6 recites the limitation "oncogenes" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 is vague and indefinite as it employs improper Markush language because the word "and" before the final group member is lacking.

Claim 15 recites the limitation "wherein the expression vector is driven by a promoter" which is vague and indefinite. A promoter drives expression of a gene not of a vector. Claim 15 also recites "strong viral promoters" and "hybrid promoters" which are vague and indefinite as they are not defined in the specification and are not terms of art.

Claim 17 is vague and indefinite as it employs improper Markush group language. Specifically, it recites multiple "ands" and employs the use of "or".

Claim 18 is vague and indefinite as it employs improper Markush group language. Specifically, it lacks "consisting" after the word "group" on line 1 and the word "and" before the final group member is lacking.

Claim 19 recites the limitation "the recombinant cells" in line 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 21 recites the limitation "the primary and secondary" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 24 and 30 are vague and indefinite because they recite the limitation "wherein the cells are subjected to a spontaneous genetic modification" however it is unclear when in the method this step is to occur.

Claim 25 is vague and indefinite as it lacks a step which clearly relates to the preamble.

Claims 25 and 30 recite the phrase "non-tumorigenically grafting cells" which renders the claims vague and indefinite as the phrase is not a term of art and not clearly defined in the specification. It would be remedial to amend the claim language to recite "grafting non-tumorigenic cells" if that is Applicant's intent in these claims.

Claims 26, 28 and 29 are directed to "the methods of claim 25" which is vague and indefinite as claim 25 recites a single method, not a plurality of methods.

Claim 29 is vague and indefinite as it employs improper Markush group language. Specifically, it recites multiple "ands".

Claim 30 is vague and indefinite as it lacks a step which clearly relates to the preamble.

Claim 34 is vague and indefinite because it is directed to "the cell line of claim 25" however claim 25 is directed to a method, not a cell line.

Claim 35 is vague and indefinite as it is unclear if both the limitations are required for the invention or if one or the other is required for the invention. It would be remedial to amend the claim language with the word "and", "or" or "and/or" as is appropriate. In addition, the limitation "wherein the cells are subjected to a spontaneous genetic modification leading to an extended life-span" makes the claim vague and indefinite as it is unclear if Applicant intends to claim a product-by-process or a method.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 34 has been examined assuming its proper dependency is on claim 31.

18. Claims 1, 9, 12, 13, 15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Bodnar et al (Science (1998) 279:349-352). Bodnar et al teaches a human retinal pigment epithelial cell line comprising cells comprising a recombinant polynucleotide comprising the human telomerase reverse transcriptase gene (hTRT), and a method of making such a cell line. The hTRT is located on an expression vector which is a plasmid, and expression of hTRT is driven by a viral promoter (myeloproliferative sarcoma virus). The cells have normal karyotype and do not exhibit evidence of tumorigenicity. See entire document, especially p. 351 and note 19.

19. Claims 1, 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Dunn et al. Dunn et al teaches a human retinal pigment epithelial cell line (ARPE-19) which arose spontaneously having increased growth potential and normal karyotype. The cells are not transformed. See entire document, especially Abstract, p. 159 "General Properties of the ARPE-19 Cell line" and p. 165, 2nd column, 1st full paragraph.

20. Claims 1-6, 9 and 19 rejected under 35 U.S.C. 102(b) as being anticipated by Dutt et al (Oncogene (1990) 5:195-200). Dutt et al teaches a human retinal pigment epithelial cell line comprising cells comprising a recombinant polynucleotide comprising an oncogene (SV40 large T antigen, c-myc, HA-*ras* or adenovirus E1A gene), and a

method of making such a cell line. See entire document. In the absence of evidence demonstrating tumorigenicity, it is assumed the disclosed cell line is not tumorigenic.

21. Claim 35 rejected under 35 U.S.C. 102(b) as being anticipated by Manuelli et al (Diab. Nutr. Metab. (1995) 8: 281-291). Manuelli et al teaches a bovine retinal endothelial cell line wherein the cell line arose due to spontaneous mutation and the cells exhibit an extended life-span. In the absence of evidence demonstrating tumorigenicity, it is assumed the disclosed cell line is not tumorigenic.

Claim Rejections - 35 USC § 103

22. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

23. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 1, 9, 12-16, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodnar et al. Bodnar et al is applied as above. Bodnar et al does not explicitly disclose the cell line wherein the expression vector is a viral vector selected from the group consisting of LTR-based MFG, LXSN, LNSX, LNCX, lentivirus or adeno-associated virus; the cell line wherein the cells of the cell line comprise an expression vector comprising a polynucleotide coding for a therapeutic polypeptide; or a method of producing a polypeptide to treat primary or secondary ophthalmologic or neurological disorders. The choice of viral vector for expression is obvious to one of ordinary skill in the art, and would depend on the availability of viral vectors and the type of mammalian cell line one was working with. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to develop the cell line comprising an expression vector comprising a polynucleotide coding for a therapeutic polypeptide, and to use the cells in a method to produce therapeutic polypeptides because Bodnar et al suggest it (p. 352). One of ordinary skill in the art would have been motivated to do so because of the potential value to the pharmaceutical industry as well as to research and medicine.

25. Claims 1, 9, and 12-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodnar et al as applied to claims 1, 9, 12-16, 19 and 20 above, and further in view of Litchfield et al. Bodner et al does not explicitly teach the types of therapeutic polypeptides that could be expressed in the mammalian retinal pigment cell line. Litchfield et al teach the use of cytokines such as bFGF, aFGF, BDNF, CNTF and IL1-β, and factors for blocking apoptosis, as therapeutic factors for degenerative retinal

diseases, such as macular degeneration and retinitis pigmentosa. See pp.657 and 662. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to combine therapeutic factor teachings of Litchfield et al with the cell line and methods of Bodnar et al. One of ordinary skill in the art would have been motivated to do because both references teach the use of cell lines for retinal disease therapy and there would be great medical and capital value associated with such a product and a method.

26. Claims 1-6, 9, 19 and 36 rejected under 35 U.S.C. 103(a) as being unpatentable over Dutt et al. Dutt et al is applied as above. Dutt et al does not explicitly teach a method for making a retinal endothelial cell line. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the method for making a mammalian retinal pigment epithelial cell line taught by Dutt et al to make a mammalian retinal endothelial cell line, and specifically, a rat retinal endothelial cell line. One of ordinary skill in the art would have been motivated to do so because Dutt et suggest the use of their method for establishing cell lines from different ocular tissues (p. 198, 2nd paragraph of Discussion) and state that there are very few established cell lines available from ocular tissue (1st paragraph of Discussion). The choice of a rat cell line rather than the human cell line taught by Dutt et al is a matter of convenient and ready access to rat eyes compared to the difficulty of obtaining a human donor eye.

Conclusion

No claims are allowed. Claims 8, 10, 24, and 33 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 8:30 AM to 5:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Richard Schwartz, can be reached on (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

March 25, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER